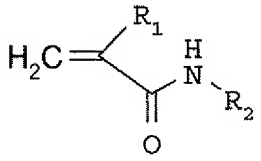
AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,

- an acryloyl distamycin derivative of formula (I):

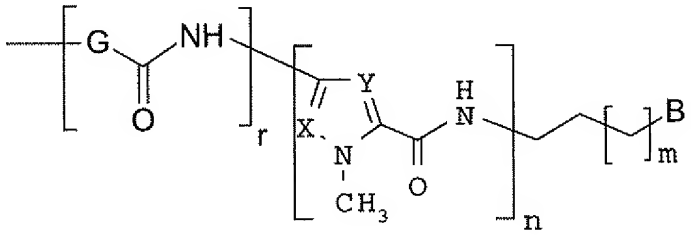


(I)

wherein:

R_1 is a bromine or chlorine atom;

R_2 is a group of formula (II)



(II)

wherein

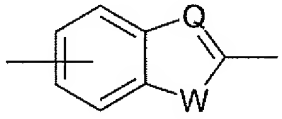
m is an integer from 0 to 2;

n is an integer from 2 to 5;

r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

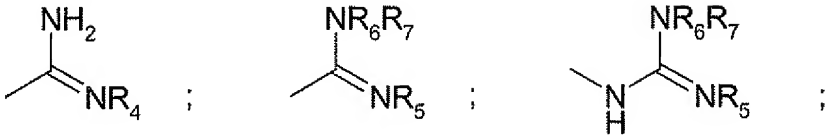
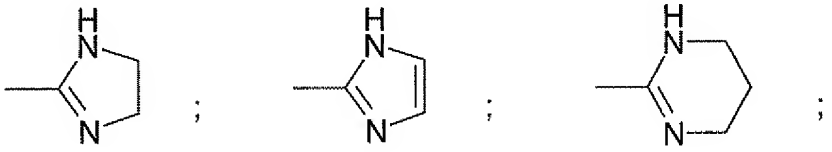
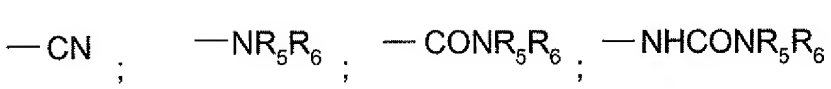
G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



(III)

wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR_3 wherein R_3 is hydrogen or C_1-C_4 alkyl;

B is selected from the group consisting of

wherein R_4 is cyano, amino, hydroxy or C_1-C_4 alkoxy; R_5, R_6 and R_7, the same or different, are hydrogen or C_1-C_4 alkyl; or a pharmaceutically acceptable salt thereof; and

a protein kinase inhibitor; wherein said pharmaceutical composition has a synergistic antineoplastic effect.

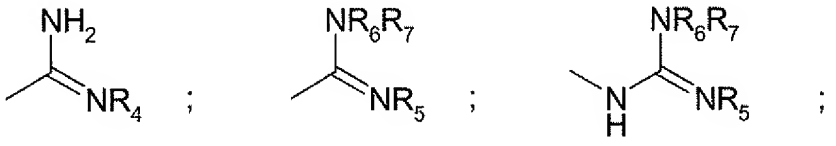
2. (Currently Amended) A pharmaceutical composition according to claim 1 wherein the protein kinase inhibitor is selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-), PKI 166(Phenol, 4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-), EKB-569(2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-,(2E)-), GW572016(4-Quinazolinamine, N-[3-chloro-4-[(3-fluorophenyl)methoxyl]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-), CEP 2563(β-Alanine, L-lysyl-,[(9S,10S,12R)-2,3,9,10,11,12-hexahydro-10-methoxy-9-methyl-1-oxo-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-I][1,6]benzodiazocin-10-yl]methyl ester, hydrochloride (1:2)), UCN-01(9,13-Epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-1-one,2,3,10,11,12,13-hexahydro-3-hydroxy-10-methoxy-9-methyl-11-(methylamino)-,(3R,9S,10R,11R,13R)-), [[G]]CGP 41251 ~~(STI 412)~~(Benzamide, N-[(9S,10R,11R,13R)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-

1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-N-methyl-), Safingol(1,3-Octadecanediol, 2-amino-, (2S, 3S)-), Perifosine(Piperidinium, 4-[[hydroxy(octadecyloxy)phosphinyl]oxy]-1,1-dimethyl-, inner salt), SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-), CGP 79787(1-Phthalazinamine, N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-), CP-564959, ZD 6474(4-Quinazolinamine, N-(4-bromo-2-fluorophenyl)-6-methoxyl-7-[(1-methyl-4-piperidinyl)methoxyl]-), ZD 2171, SU-11248(Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoror-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1)), Flavopiridol(4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-), and CI-202.

3. (Currently Amended) A pharmaceutical composition according to claim 2 wherein the protein kinase inhibitor is selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-) and SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-).

4. (Cancelled)

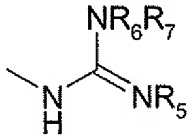
5. (Previously Presented) A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative of formula (I) wherein R_1 and R_2 are as defined in claim 1, r is 0, m is 0 or 1, n is 4, X and Y are both CH groups and B is selected from:



$$-CN \; ; \; -CONR_5R_6 \; ; \; -NHCONR_5R_6$$

wherein R_4 is cyano or hydroxy and R_5, R_6 and R_7, the same or different, are hydrogen or C_1-C_4 alkyl.

6. (Original) A pharmaceutical composition according to claim 5 comprising an acryloyl distamycin derivative of formula (I) wherein R_1 is bromine, R_2 is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula



wherein R_5, R_6 and R_7 are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt.

7. (Previously Presented) A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative, optionally in the form of a pharmaceutically acceptable salt, selected from the group consisting of:

N-(5-{[(5-{[(5-{[(2-{[amino(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(5-{[(5-{[(2-{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(5-{[(5-{[(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(5-{[(5-{[(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-imidazole-2-carboxamide hydrochloride;

N-(5-{[(5-{[(5-{[(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide hydrochloride;

N-(5-{[(5-{[(5-{[(3-amino-3-oxopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide;

N-(5-{[(5-{[(5-{[(2-{[amino(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

N-(5-{[(5-{[(3-{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

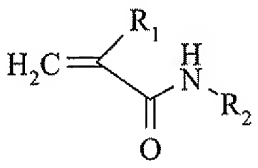
N-(5-{[(5-{[(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride; and

N-{5-[({5-[({5-[({3-[(aminocarbonyl)amino]propyl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}amino)carbonyl]-1-methyl-1H-pyrrol-3-yl}-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide.

8. (Currently Amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,

- N-(5-{[(5-{[(5-{[(2-{[amino(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin); and
- a protein kinase inhibitor selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-), and SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-).

9. (Previously Presented) Product comprising an acryloyl distamycin derivative of formula (I):

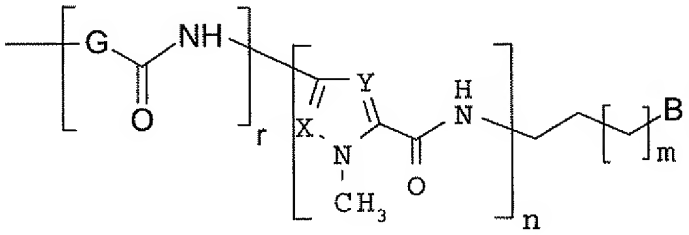


(I)

wherein:

R_1 is a bromine or chlorine atom;

R_2 is a group of formula (II)



(II)

wherein

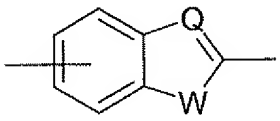
m is an integer from 0 to 2;

n is an integer from 2 to 5;

r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:

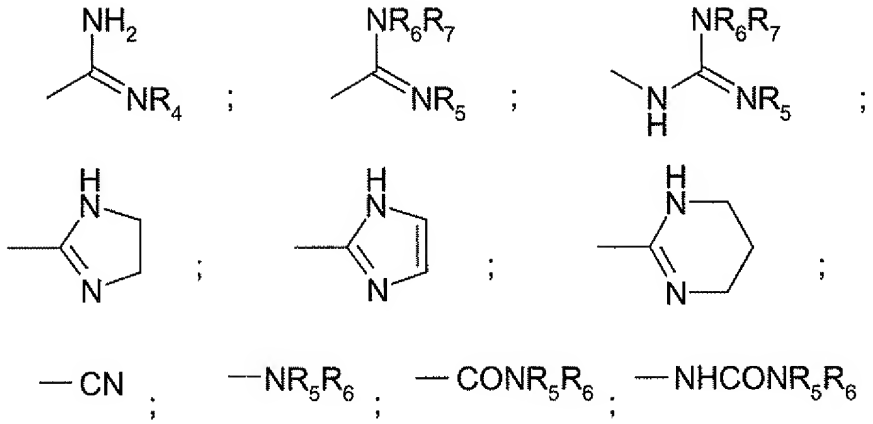


(III)

wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR_3;

wherein R_3 is hydrogen or C_1-C_4 alkyl;

B is selected from the group consisting of



wherein R_4 is cyano, amino, hydroxy or C_1-C_4 alkoxy; R_5, R_6 and R_7, the same or different, are hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof; and

a protein kinase inhibitor, as a preparation where the acryloyl distamycin derivative may be administered simultaneously with the protein kinase inhibitor or, alternatively, both compounds may be administered sequentially in either order in the treatment of tumors.

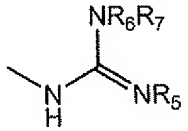
10. (Currently Amended) The [[P]] product according to claim 9 wherein the protein kinase inhibitor is selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-), PKI 166(Phenol, 4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-), EKB-569(2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-,(2E)-), GW572016(4-Quinazolinamine, N-[3-chloro-4-[(3-fluorophenyl)methoxyl]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-), CEP 2563(β-Alanine, L-lysyl-,[(9S,10S,12R)-2,3,9,10,11,12-hexahydro-10-methoxy-9-methyl-1-oxo-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-I][1,6]benzodiazocin-10-yl]methyl ester, hydrochloride (1:2)), UCN-01(9,13-Epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-1-one,2,3,10,11,12,13-hexahydro-3-hydroxy-10-methoxy-9-methyl-11-(methylamino)-,(3R,9S,10R,11R,13R)-), [[G]]CGP 41251 ~~(STI 412)~~(Benzamide, N-[(9S,10R,11R,13R)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-N-methyl-),

Safingol(1,3-Octadecanediol, 2-amino-, (2S, 3S)-), Perifosine(Piperidinium, 4-[[hydroxy(octadecyloxy)phosphinyl]oxy]-1,1-dimethyl-, inner salt), SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-), CGP 79787(1-Phthalazinamine, N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-), CP-564959, ZD 6474(4-Quinazolinamine, N-(4-bromo-2-fluorophenyl)-6-methoxyl-7-[(1-methyl-4-piperidinyl)methoxyl]-), ZD 2171, SU-11248(Butanedioic acid, 2-hydroxy-, (2S)-, compd. with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoror-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1)), Flavopiridol(4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-), and CI-202.

11. (Currently Amended) The [[P]] product according to claim 10 wherein the protein kinase inhibitor is selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxyl-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-) and SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-).

12. (Cancelled)

13. (Previously Presented) Product according to claim 9 comprising an acryloyl distamycin derivative of formula (I) wherein R_1 is bromine, R_2 is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula



wherein R_5, R_6 and R_7 are hydrogen, optionally in the form of a pharmaceutically acceptable salt.

14. (Previously Presented) Product according to claim 9 wherein the acryloyl distamycin derivative is selected from the group as defined in claim 7.

15. (Currently Amended) Product comprising the acryloyl distamycin derivative N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and a protein kinase inhibitor selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-) and SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-); as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

16.-23. (Cancelled)

24. (Currently Amended) A method of treating a mammal, ~~including humans,~~ suffering from a neoplastic disease state, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

25. (Currently Amended) A method according to claim 24 wherein the acryloyl distamycin derivative is N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-) and SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-).

26. (Currently Amended) A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent, in a mammal in need thereof ~~including~~

~~humans~~, the method comprising administering to said mammal a combined preparation comprising a protein kinase inhibitor and an acryloyl distamycin derivative of formula (I), as defined in claim 1, in amounts effective to produce a synergistic antineoplastic effect.

27. (Currently Amended) A method according to claim 26 wherein the acryloyl distamycin derivative is N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571(Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-), ZD-1839(4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-), OSI-774(4-Quinazolinamine, N-(3-ethynylphenyl)-6, 7-bis(2-methoxyethoxy)-) and SU 5416(2H-indol-2-one, 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1, 3-dihydro-).

28. (Previously Presented) A method according to claim 24 wherein said disease state is selected from breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors.

29. (Currently Amended) A method of treating metastasis suffered by a mammal, ~~including humans,~~ which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

30. (Currently Amended) A method of treating tumors in a mammal, ~~including humans~~ by inhibition of angiogenesis, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

31. (New) The method of treating a mammal according to Claim 24 wherein the mammal is human.

32. (New) The method for lowering the side effects according to Claim 26 wherein the mammal is human.

33. (New) The method of treating metastasis suffered by a mammal according to Claim 29 wherein the mammal is human.

34. (New) The method of treating tumors in a mammal according to Claim 30 wherein the mammal is human.